

### III

## THE VACCINE THERAPY OF GONOCOCCAL INFECTIONS

A discussion based upon papers read by PROF. J. W. H. EYRE and DR. DAVID THOMSON before the Society on February 27, 1925.

THE PRESIDENT said the discussion promised to be an animated one, and it would be agreed that both the openers had given members much to think about. It was now realised that the vaccine therapy of gonorrhœa was not so simple a matter as putting into the patient doses according to the directions given by some enterprising chemists. He would give his own remarks on the subject at the end of the discussion.

Dr. DAVID WATSON said that he used vaccines fourteen years ago, and then he employed autogenous, also mixed, vaccines. In those early days he thought he had made a discovery of value, namely, giving a small injection of about  $2\frac{1}{2}$  millions, and taking smears twenty-four or forty-eight hours later, and finding gonococci abundant where previously they had been deficient. He thought then that the vaccine might be used as an aid to diagnosis. As had since been confirmed, that method of making the diagnosis made the patient worse.

He assured himself at that date that vaccines had an effect, and he considered they ought to be of value if enough were known about them to control their effects to the advantage of the patient. He felt the need for more knowledge than he either possessed or could cull from the literature on the subject.

Since then his attitude had been that of waiting for the kind of papers which had been contributed to-night, and he congratulated both the readers and also the Society on having had the papers. But what could he carry home for practical use in his work? Not very much, he feared, unless the subsequent discussion brought conviction to his mind. At present he left it to his house-surgeon to either use vaccines or not, as he wished, *i.e.*, detoxicated vaccines, as he considered they were the more safe. Ordinary vaccines were dangerous, not to the patient's

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health, but in prolonging the convalescence and making the treatment of the chronic infections more difficult.

Professor Eyre had spoken of the different strains of gonococci, and had suggested that the use of an auto-genous vaccine would overcome the difficulty due to this. If there were so many strains, why should only one strain be present in one infected patient? The organism from the joints might differ from that from the conjunctiva, or from the urethra. The difference might only be one due to subculture.

There were many points in this subject to be considered, not only from the bacteriologist's point of view, but also from the physician's. The gonococcus was bathed not in serum, but in gland secretion, and in the latter he did not know that one could expect antibodies to be present. Vaccine treatment could not be expected to have effect on organisms which were not embedded in tissues.

He was very pleased that such good work was being done on the subject, and he hoped it would lead to an early solution of the difficulties.

Dr. J. C. BUCKLEY said it was now twenty years since he began to give vaccines in the treatment of gonorrhœa, using those prepared by Parke Davis & Co. In 1916 he was at Lichfield in charge of some officers, and one of them was very ill with gonorrhœal rheumatism. He procured some Army vaccine, and it gave surprisingly good results; it transpired, from a conversation he had with Colonel Harrison, that it was obtained from some virulent cases at Havre.

As soon as detoxicated vaccine was started he began to use it, and very largely, and on the whole he had very good results. But it was very difficult to know whether vaccine treatment was efficacious or not, unless one had time to properly analyse one's cases. In cases with a secondary infection detoxicated vaccine had been very valuable, also in some cases of prostatitis. He had himself had a non-gonococcal arthritis of the knee, and the removal of some teeth and the use of an autogenous streptococcal vaccine had worked wonders.

For six months he had ceased to use detoxicated vaccine for gonorrhœa in the early stage, continuing it for the old-standing cases. He hoped that some day he would go through his results and say something about them. In all cases for which he used detoxicated vaccine

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the reaction was very slight, and he worked up to 50,000 millions.

Major A. T. FROST said the discussion showed that the profession was still groping in the dark on this subject. Professor Eyre had stated the difficulties as most of the members felt them. Stock vaccines were still in a very anomalous position ; one did not know what one was using, nor the age of the preparation. At the Royal Herbert Hospital—the successor to Rochester Row—rather poor results were being obtained with vaccines for some time, and that was because old cultures were being used. A change took place when cultures of not more than two or three generations were employed. With stock cultures one was in doubt about dosage. If manufacturers of stock vaccines would guarantee a golden mean, there would probably be better results among users.

Professor Eyre had asked a question about Besredka's work in gonorrhœa. At the hospital the effect of small doses of the wash of gonococcus, untouched, had been tried, and he felt that there had been a distinct improvement in the cases ; that injecting into the urethra 10 or 20 millions, and tying them in, leaving them ten to twenty minutes, was a distinct advance in urethral gonorrhœa. Some dried up after the first or second injection.

With regard to detoxicated vaccines, before he left Rochester Row a certain number of cases were treated on Dr. David Thomson's plan, and he feared they were not able to get the favourable results Dr. Thomson had.

He thought the profession was getting away from the important point in the days of Pasteur, who gave living microbes, which were detoxicated in the normal way, *i.e.*, by growing them under conditions which did not interfere with their delicate protein. Then Wright gave the "killed" vaccine, which was not so satisfactory, but which was the practical way. A third way was that mentioned to-night by Dr. Thomson, *i.e.*, detoxication by getting rid of the toxins by chemicals. He thought it desirable to go back to the days of Pasteur, and give living toxin, for nothing which could be given in the manufactured state would equal Nature's method. The gonococcus differed from most other organisms in that it had a small response, and the tissues were not in a position to react. Could one look forward hopefully to

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the day when the methods of growth and of changing the toxicity by natural methods would constitute the way out of the difficulty by which the subject was surrounded ?

Dr. Watson had said he did not like to see his chronic cases becoming acute ; but he, the speaker, thought acute cases were more easily cured than chronic ones.

Major LAMBKIN said that for some time he and his colleagues had been trying local injections of ecto- and endo-toxin in the acute stages of gonorrhœa. They were giving small doses at present, and it was combined with electrical treatment. The results with this colloid *plus* some buffer like an ecto- or endo-toxin had been encouraging in the last few months. They were employing endo-toxin corresponding to 250 millions of gonococcal endo-toxin as a test of cure. They now gave silver nitrate and magnesium chloride, and the best test of cure was the endo-toxin. It was held in the urethra half an hour, and if anything active remained there, in the course of two or three days there would be evidence of it in the anterior urethral smears. He did not think he had ever seen it fail. He agreed that in a long series there were better results after using vaccines than from non-vaccine treatment, especially in cases with complications. But he felt that each case and each particular vaccine should be studied. No two brews of polyvalent vaccine had the same effect, and one should try quietly until one found what effect was being produced in the particular patient.

Major FRENCH said that many years ago, in India, he tried vaccines in the treatment of gonorrhœa, and he found that the toxicity was greatly increased. He confined the vaccine treatment to subacute cases, then he got better results, and he continued the method for some years. When Dr. Thomson brought out his detoxicated vaccine, he, the speaker, was in charge of a large clinic in France, and he treated a series of cases with the ordinary toxic vaccine, and others with detoxicated vaccine, and the latter showed the better results ; there was a saving of about seven days.

Dr. MARGARET RORKE said her experience in this matter was limited to stock vaccines made in the Royal Free Hospital, from gonococcal discharge in small children. It gave fairly good results in subacute or fairly old cases, in which one felt the need of a supplement to the local

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treatment. Old-standing cases, of twenty years or so, derived no benefit from vaccines. In those, other organisms, such as staphylococci and diphtheroids, were frequently found. She was in despair when she began to use non-specific protein, with electrargol ; then the results got much better. Some patients got, almost immediately, vaso-motor reaction. During the last three months she had had encouraging results from milk protein injections, especially in chronic cases in women.

Dr. DOROTHY LOGAN said that when she was using vaccine she found that the cases seemed to improve clinically if a large dose were given, and she reached 500 millions towards the end of the course. She believed Professor Eyre showed that this would over-sensitise the patients, and that therefore it was not the right thing to do. She started with  $2\frac{1}{2}$  millions, and went up gradually. Subsequently she used a vaccine prepared for her by Dr. Roche, and she concluded that the cases in women and children cleared up better after the vaccine ; she therefore gave it as a routine in clinically positive cases. She went up to a dose of 1,000 millions, giving a steadily increased dose once a week, the progression being  $2\frac{1}{2}$ , 5, 10, 50, 100, then by hundreds. In some cases recently she had been more drastic, starting with 5 millions, then going to 20, 100, and then by hundreds ; she then got better and quicker results. It was after a dose of 100 or 200 millions that a distinct difference was noticed in the patient. Sometimes the earlier doses did not seem to have enough effect. She had the temperatures taken regularly, and she did not remember more than two cases of increased temperature in a whole course. In one child she was compelled to proceed by 50's, but with the rise in temperature there were no bad symptoms. Sometimes there was thought to have been a little more discharge two days after the injection. Dr. Roche said he made the vaccine very carefully from many different strains, and washed away the serum which he used to assist the organisms to grow, and Dr. Roche thought the absence of reaction was due to that. For two years, at King's College Hospital, she had used detoxicated vaccine, starting with a dose of 1,000 millions, and going up to 10,000 millions. She decided that she did not get better results with that than with the ordinary stock vaccine. She was now using a stock vaccine of the ordinary toxic

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type, which Dr. Roche was preparing for her. To one woman she was giving detoxicated vaccine, and she got better in course of time, but she reported that she had again become pregnant. She therefore told the woman to come to her once a fortnight during her pregnancy. She looked well all the time, and the speaker wrote to another hospital stating she thought this woman could be taken into the general ward for her confinement. This was done. Six weeks after the confinement the woman came back, still looking well, but gonococci were still found. She had had detoxicated vaccine, no other kind.

Dr. C. MILLS said that, in his opinion, the only way to form a judgment in this matter was to study and compare large series of cases of all types, one series treated with routine vaccines, the other without. His view was that routine employment of vaccines diminished the incidence of complications. A main necessity was to study the idiosyncrasies of the patient. He had recently tried treating vaccine with ozone to see if that lessened the toxicity. At first he tried two patients. One stood up to tremendous doses, *i.e.*, 100,000 millions, but the other could not tolerate 2,000 millions; he was ill for three or four days. Thus no definite rule as to dosage could be laid down; it was necessary to gently feel one's way in each case, being guided by the general, local and focal reactions.

He was much interested in the remarks concerning the application of an emulsion over the lesion. His own feeling was that if such an emulsion were put into the urethra, it was adding a toxin to which the urethral mucous membrane had already shown a marked intolerance. He agreed it was an excellent test of cure, since there was a chance in this way of bringing the gonococci to the surface.

He had tried the effect of injecting vaccine into the tissues locally, since he thought that by this means one was getting a big output of the antibody produced *in situ*. In some cases he had injected the vaccine subcutaneously at the anterior portion of the fossa navicularis, and then the antibodies were probably conveyed along the local lymphatics. He had not seen bad results from local treatment.

Dr. DOBLE said he had heard that very good strains of gonococcus were obtained from Havre. In Uganda,

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before the war, the type of disease was very different from that here ; practically every patient had chordee, and there was much pain in passing water. It would be a good idea to get a supply of gonococci from Uganda, and try the effect of vaccines made from them. He did not think the statistics in regard to ordinary vaccines had yet been worked out properly. He did not know whether the complement-fixation test had been used, or the result of provocative doses.

The PRESIDENT said the Society was greatly indebted to Professor Eyre and Dr. Thomson for having provoked this good discussion. He was sure it was of a higher tone than one which he read in a Continental paper on the same subject. The speakers in that debate expressed either their belief or their non-belief in vaccines, and left the matter there, without giving reasons or attempting to explain bad results.

He wished to declare his own belief, which he had held for a long time, that there was good in the vaccine therapy of gonorrhœa. He had an excellent opportunity of studying it at Rochester Row in co-operation with Major Harold. Their conclusion was that the vaccine-treated case, on the whole, pursued a milder course and was freer from complications than the case treated without vaccines. He admitted that in some cases the administration of vaccine was followed by an exacerbation of symptoms, but he did not regard this as an indication that the patient had been made worse thereby. The case which cleaned up best was not always that which ran a mild course from the beginning. One of the worst things which could happen to a case of gonorrhœa was that the tissues should sit down to a truce with the gonococcus too early in the fight, relinquishing the struggle to throw out the invading organism. Increasing discharge soon after giving the vaccine showed that the tissues had been stimulated to throw the invader out. But in this problem there were streaks of good and of bad fortune, and while listening to the discussion a story came into his mind. A foreign warship put into Valetta Harbour to have her hull cleaned. For international reasons, though the bill for the previous cleaning had not been paid, they decided to do it, but as economically as possible. Therefore they scraped up all the odds and ends of anti-fouling mixture they could find for the purpose, and applied the result to

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the hull. Later she returned for another cleaning, and every one was surprised how clean she had kept. Ever since then they had been trying to discover what were the ingredients of the mixture they had used! In the same way, people who used vaccines were continually trying to discover how they got good results, and what was lacking when the results were bad. Clinicians might co-operate with pathologists in this matter by taking careful notes.

Two factors had to be dealt with: the seed and the soil. There was a great difference in the matter of the seed, *i.e.*, between the strains of gonococci in regard to their immunising effect: it might be the treatment of the seed, it might be its natural qualities, or perhaps both. Help might be afforded in a way he had tried to start in his clinic. From a patient attending a clinic an auto-genous vaccine might be prepared, one tried on the particular patient, and notes kept of the result. He was aware that the soil was a complicating factor, but one might get from such a test a general impression of the immunising value of a strain, and if it seemed to be giving respectable results, it might be put into the stock vaccine.

With regard to the soil, he did not think there could be any doubt that patients differed in their immunity response to the same vaccine; this was seen also in the different response given by animals to the same antigen. A patient might be naturally a poor responder to the vaccine. Could that power of response be artificially stimulated? He thought it would be useful to investigate on those lines. A number of people had obtained pretty good results from using, in conjunction with vaccines, non-specific proteins and electrargol.

The experiments which were made at Rochester Row with detoxicated vaccines were as objective as it was possible to make them. When Dr. David Lees was attached to his, the speaker's, hospital for a time he asked him to act as *liaison* between Dr. Thomson and the wards, and he was convinced that bias was avoided as far as was humanly possible. He, the speaker, thought the results were good; though it was possible that in those experiments Dr. Thomson had the good fortune to hit upon a pretty good streak of immunising strains.

Professor EYRE, in reply, said the discussion had been so interesting, and had raised so many points, that he



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could start the subject all over again with advantage and benefit. At this late hour, however, he would not attempt that. He had not read his notes *in extenso*. There had been an attempt by many of the workers to correlate the clinical signs and symptoms following the inoculation of a dose of vaccine. The increase of discharge, with a larger number of gonococci, following a dose of vaccine, was well known in the laboratory, and it usually preceded a marked clinical improvement as shown by less pus and less organisms. If the dose was too big, a bad result ensued, but that should not be used as an argument against vaccines. Opium was not discarded in disease because in large doses it was dangerous.

Another point raised was the possibility of diverse strains being encountered in different situations in the same individual. So far as his experience went, that was not the case: the same strain was yielded from the conjunctival sac as from the urethra of the same person. His own opinion was that serological strains merely indicated the response of the organism to its particular environment; it got into a strange house and surroundings, and adapted itself accordingly, the difference being only minute.

He agreed that the personal equation came into play in this matter. No two persons were alike in their response to vaccines. The method used in making stock vaccines was the one the President suggested, namely, picking out those used as autogenous vaccines which gave good results. One patient would respond well to a certain dose, another would be made worse by it.

He was very interested in the experiments in which gonococcal vaccine was used locally. There was probably a future for that, as would be tested over a series. It was only by a mass investigation that information of value would be obtained.

Dr. DAVID THOMSON, in reply, said that since the work was started at Rochester Row several changes in the preparation had been made. The first vaccine they made was precipitated with weak acid, and then washed in saline. After reading Vaughan's work he thought that alcohol helped to dissolve toxins, and he was aiming to give a dose of gonococcus equalling 2 c.c. of solid substance, but he had not been able to reach that. By washing with alcohol he thought it would be less toxic.

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There were a few undissolved germs in the original detoxicated vaccine, therefore later he filtered the alkaline solution through a Berkefeldt filter. Later still, when working with sheep corpuscles injected into rabbits, he found that if one treated them with absolute alcohol and then injected, it reduced the autogenic resistance considerably. He therefore stopped the use of alcohol in the preparation of detoxicated vaccines. He believed that with the present method of making the vaccines the results ought to be better than ever.